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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1636	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/617,116	AGHI ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' amendment filed on 4/4/03 in Paper No. 15 has been entered.

Claims 14-36 are pending in the present application, and they are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 112

Claims 14-32 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of enhancing the cytotoxic sensitivity of neoplastic cells to an antifolate drug, said method comprising:

(a) **delivering directly** to said neoplastic cells a vector, said vector comprising a DNA sequence encoding folylpolyglutamyl synthetase (FPGS), operably linked to a promoter, wherein said FPGS is expressed in said neoplastic cells at a level higher than the endogenous FPGS level of said neoplastic cells; and

(b) treating the neoplastic cells in step (a) with an antifolate drug that is polyglutamated by said FPGS; whereby enhancing the cytotoxic sensitivity of said neoplastic cells to said antifolate drug,

does not reasonably provide enablement for a method of enhancing the cytotoxic sensitivity of neoplastic cells to an antifolate drug by delivering to said neoplastic cells a vector comprising a DNA sequence encoding folylpolyglutamyl synthetase (FPGS),

operably linked to a promoter **by any route of administration**, particularly the use of any replication competent viral vectors and/or pathogenic live prokaryotic vectors through a systemic delivery, or the same method using **any prokaryotic vector, particularly a prokaryotic expression plasmid vector, any pathogenic, non-attenuated live bacterial vector, or a mammalian artificial chromosome**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the same reasons already set forth in the previous Office Action in Paper No. 13 (pages 4-12).

Response to Arguments

Applicants' arguments presented in the Amendment filed on 4/4/03 in Paper No. 15 (pages 8-28) have been fully considered.

1. With respect to the issue on any route of *in vivo* vector delivery, Applicants argue that the references cited by Examiner merely set forth technical hurdles that need to overcome in order to increase the efficiency with which genetic vectors are targeted to cells *in vivo*. They do not, however, indicate that vector delivery to target cells is impossible or infeasible. Particularly, with respect to a paragraph in the Deonarain reference indicating that liver can take up 85% of the injected DNA molecule via the vascular system, Applicants argue that Applicants' claims do not exclude the sensitization or killing of liver cancer cells and that the Deonarain reference is an exemplary publication where gene delivery was successful without requiring direct

inoculation. With respect to the Xu reference, Greco reference and Dachs reference, Applicants argue that the authors cited numerous positive reports, and that the described results are encouraging and that they illustrate both feasibility and future promise for GDEPT as a cancer treatment. Applicants also rely on the statement "Recent studies have reported significant success in improving the *in vivo* performance of nonviral gene delivery system" of Romano, and the statement "one might rather consider these data as encouraging" in regarding to the discussion of *in vivo* gene transfer by lipolexes of Scherman et al., as evidences that the present application is full enabled for the methods as claimed. Applicants further argue that Applicants' claims do not require that the vector carrying the FPGS gene be delivered into neoplastic cells with any particular minimum level of efficacy, particularly for a gene delivery system utilizing so called "suicide genes", such as FPGS, wherein only a low level of gene delivery is required to exert anti-neoplastic effects. Additionally, one of the advantages of FPGS gene therapy is that the gene product expressed by the tumor cells (FPGS) is not a foreign enzyme as might be the case with expression of foreign suicide gene such as HSV thymidine kinase, bacterial cytosine deaminase, an therefore should not elicit an immune response. Applicants' arguments are respectfully found to be unpersuasive for the following reasons.

Firstly, even in 2001 reviews on gene directed enzyme/prodrug cancer therapy by Xu et al. and Greco et al. clearly indicate that the lack of an efficient gene delivery to targeted cells still remains a major problem to attain therapeutic efficacy, let alone at the filing date of the present application. The instant specification fails to provide any

guidance, particularly any relevant *in vivo* example demonstrating that any vector comprising a DNA sequence encoding FPGS can be delivered efficiently to neoplastic cells by any route of delivery, particularly via a systemic delivery, to attain the desired therapeutic effects. Positive and/or encouraging statements that Applicants vaguely refer to are not indications that obstacles in vector targeting *in vivo* for attaining therapeutic effects have been overcome, and that the problems are routine technical hurdles. It is also noted that the claims encompass a method of enhancing the cytotoxic sensitivity of neoplastic cells occurring at any site, not necessarily in the liver. Given the state of the art and with the lack of sufficient guidance provided by the present application, naturally it would have required undue experimentation for a skilled artisan to make and use the methods as claimed.

Secondly, it should be noted that a mimimal threshold level of neopastic cells must be transfected or transformed with a vector comprising a DNA sequence encoding FPGS, so that the genetically modified neoplastic cells become more sensitive to an antifolate drug to yield the desired therapeutic effects such as decreasing a tumor load or inhibiting tumor growth by enhanced killing of neoplastic cells directly or indirectly (by-stander effects). The instant specification fails to provide sufficient guidance for a skilled artisan on how to obtain the threshold level of transfected or transformed neoplastic cells using a vector comprising a DNA sequence encoding FPGS by any route of delivery, particularly via a systemic delivery system.

Thirdly, an adverse host immune response is elicited against administered vectors (prokaryotic vectors, viral vectors particularly adenoviruses, liposomes, cationic

peptides) comprising a DNA sequence encoding FPGS, rather than the FPGS enzyme (an intracellular enzyme), that results in an inefficient delivery of the vectors to the target cells to yield the desired therapeutic effects.

2. With respect to the issue of using any prokaryotic vectors, Applicants argue that apart from the teachings of Pawelek et al. on the use of attenuated strains of Salmonella as tumor targeted bacterial vectors, Lemmon M.J. (Gene therapy 4:791-796, 1997) teach the use of anaerobic bacterial as a systemic gene delivery system that is controlled by the tumor microenvironment, and therefore the present application is fully enabled for the methods as claimed. Additionally, Examiner has not cited any objective evidence or provided sound scientific reasoning to doubt the enablement of prokaryotic vectors as a means of gene delivery. Applicants' arguments are respectfully found to be unpersuasive for the following reasons.

Firstly, as written the claims encompass any prokaryotic vector such as a prokaryotic expression plasmid vector and a live bacterial vector. Attenuated strains of Salmonella taught by Pawelek belong to the later. The instant specification fails to provide any guidance for a skilled artisan on how to use any prokaryotic expression plasmid vector in the method as claimed. It is absurd that a prokaryotic expression plasmid vector can be expressed in a eukaryotic cell such as a neoplastic cell as encompassed by the scope of the instant claims. This is contrary to what is known in the art.

Secondly, apart from a cursory mentioning of an attenuated *Salmonella* anticancer vector taught by Pawelek et al., the instant specification fails to provide sufficient guidance for a skilled artisan on how to make and use of any other live bacterial vectors in the methods as claimed. There are several factors that need to be considered here, such as whether any prokaryote is capable of invading a neoplaastic or tumor cell? Whether any prokaryote can survive, grow and proliferate in a neoplastic or tumor cell under both anaerobic and aerobic conditions as found within a solid tumor? How does any prokaryote specifically target a neoplastic or tumor cell in an efficient number to mediate the desired therapeutic effects? Lemmon et al. teach the intravenous injection of an inactive spore form of *Clostridium beijerinckii* into a tumor mouse model, not the use of any prokaryotic vector or any live bacterial vector. Furthermore, there is no literal support in the present application that Applicants even contemplate using an inactive spore form of any bacteria as a gene delivery system. Applicants are invited to point out the specific page number, line number of the specification for such a support.

3.. With respect to the issue of using replication competent viral vectors and/or pathogenic live prokaryotic vectors, Applicants directed Examiner to the sentence "However, when attenuated, hyperinvasive autotrophic mutants were used, the tumor targeting and amplification phenomena were retained, whereas their pathogenicity was limited". Additionally, Applicants submit a review article of Galanis and Vile (Crit. Rev Oncol Hematol 38:177-192, 2001) focusing on the use of targeting and replication

competent vectors to overcome challenges in gene therapy. Applicants' arguments are respectfully found to be unpersuasive for the following reasons.

Firstly, Pawelek et al. clearly state "When wild-type *Salmonella* were introduced into melanoma-bearing mice, the bacteria were found within the tumor....., although as pathogens, they cause the death of the mice" (see abstract). Then, given the lack of sufficient guidance provided by the present application, how can a skilled artisan use a wild-type *Salmonella*, or any pathogenic live prokaryotic vectors for gene delivery in the methods as claimed to attain the desired therapeutic results, particularly through a systemic delivery?

Secondly, although the review article Galanis and Vile teach the use of replication competent viral vectors to improve the efficiency of gene transfer, nowhere in the review article one can find that such replication competent viral vectors are delivered through a systemic approach (other than intratumoral injections) for cancer gene therapy. Neither does the instant specification.

4. With respect to the issue of using mammalian artificial chromosomes, Applicants presented essentially the same arguments as those in the Amendment filed on 9/20/02 in Paper No. 12 (pages 19-23). Applicants' arguments are respectfully found to be unpersuasive for the same reasons already stated in the previous Office Action (pages 17-19).

Claim Rejections - 35 USC § 103

Claims 14-27 and 30-35 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Moscow et al. (U.S. Patent 5,763,216) in view of Roy et al. (J. Biol. Chem. 272:6903-6908, 1997; IDS); Kim et al. (J. Biol. Chem. 268:21680-21685, 1993; PTO-1449, AS) and Garrow et al. (Proc. Natl. Acad. Sci. 89:9151-9155, 1992; PTO-1449, AR) for the same reasons already set forth in the previous Office Action in No. 13 (pages 20-25).

With respect to the enabled scope of the presently claimed invention and the elected species, Moscow et al teach a method of inhibiting the growth of a tumor in a mammal comprising the steps of administering directly into methotrexate-resistant, transport-deficient cancer cells a vector containing the gene encoding a human reduced folate carrier (RFC), and administering methotrexate to the mammal to enhance the efficacy of traditional methotrexate chemotherapy (see Summary of the Invention, particularly section 3 in cols. 6-9). Moscow et al. teach that appropriate viral vectors such as retrovirus vectors, adenovirus vectors and adeno-associated virus vectors can be used to deliver the gene encoding RFC into a MTX-resistant, transport-deficient cancer cell (col. 7, lines 18-24). Additionally, other recombinant vectors containing the gene encoding RFC can be achieved by any of the methods well-known in the art (col. 6, lines 45-54). Moscow et al. further teach that a short-coming of MTX (a folate antagonist) drug therapy is that previously responsive tumors (e.g. non-Hodgkin's lymphoma, child-hood acute lymphoblasti leukemia, osteosarcoma and breast cancer) can become refractory to MTX after continued exposure. Resistance to MTX in *in vitro* models can result from over-expression of the target enzyme dihydrofolate reductase,

alteration of dihydrofolate reductase affinity for MTX, decreased folylpolyglutamate synthase (FPGS), and decreased thymidylate synthase levels, as well as decreased MTX uptake in MTX-resistant cell lines such as murine L1210 leukemia cell lines, human leukemia cell lines, CHO cells and human ZR-75-1 breast cancer cells (col. 1, lines 10-23; lines 47-56).

Moscow et al. do not specifically teach the use of a vector comprising a nucleotide molecule encoding folypolyglutamyl synthase (FPGS) into neoplastic cells to enhance the cytotoxic sensitivity of the neoplastic cells to an antifolate drug such as methotrexate, edatraxate or others.

However, at the effective filing date of the present application, Roy et al. also teach that a major limitation for cancer therapy with classical folate analogues is the acquired resistance of tumor cells to methotrexate and folate analogues (page 6903, col. 2, first full paragraph). Specifically, Roy et al. teach that *in vitro* L1210 tumor cells resistant to methotrexate have a decrease in the rate of FPGS mRNA transcript formation, resulting in lower FPGS activity (page 6907, col. 2, first full paragraph), and that L1210 tumor cells resistant to edatrexate have constitutively down-regulated steady state levels of FPGS or FPGS activity compared with parental L1210 tumor cells and that FPGS mRNA from the variant cells was significantly less effective in mediating formation of the FPGS peptide product in a manner correlating with the FPGS activity or protein (see abstract). Roy et al. further teach that resistance to classical folate analogues in the murine tumor resulting in lower FPGS activity can occur from both transcriptional and post-transcriptional alterations of FPGS gene expression (page

6907, col. 2, first full paragraph). Additionally, at the effective filing date of the present invention, Kim et al. also teach that FPGS-deficient mutant Chinese hamster ovary (CHO AUXB1) cells expressing human folylpolyglutamate synthetase (FPGS) metabolize methotrexate (MTX) to polyglutamates characteristics of human cells (see Table I, page 21681), and that upon a short term exposure to MTX (4 h or 72 h), cells expressing higher levels of human FPGS are more sensitive to the cytotoxicity of MTX compared to cells expressing lower levels of human FPGS (see Table III, page 21682). Kim et al. note that the ability of cells to metabolize MT to longer chain length derivatives enhances cytotoxicity when MTX is infused for a limited period and then removed, which mimics clinical usage, and that larger effects of FPGS activity levels on the cytotoxicity of antifolates that require polyglutamylation for effective inhibition of target enzymes were also observed (page 21683, col. 2, last paragraph). Kim et al. further teach that lowered FPGS activity may be a general mechanism by which human leukemia cells can become resistant to a wide range of antifolates (page 21684, col. 1, top 5 lines) and that decreased polyglutamylation as a mechanism for inherent MTX resistance for a number of sarcoma and squamous carcinoma cell lines even though FPGS levels appear normal (page 21684, col. 1, bottom of the second paragraph). Garrow et al. already teach the cloning of a human cDNA sequence encoding for FPGS, as well as the expression of human FPGS into the same CHO AUXB1 cells using a plasmid vector pSVK-hFPGS (see Fig. 1 and page 9152, col. 2, first full paragraph).

Accordingly, at the time of the instant invention it would have been obvious and within the scope of skills for an ordinary skilled artisan to modify the method of Moscow

et al. by direct delivery of a non-viral (plasmid) or viral vector comprising a DNA sequence encoding human FPGS into neoplastic cells *in vivo* that have acquired resistance to methotrexate and other classical folate analogues in order to reverse the resistance of MTX or other antifolate drugs in these neoplastic cells, so that to enhance the efficacy of conventional anti-folate drug therapy in light of the teachings of Roy et al., Kim et al. and Garrow et al. It is noted that as defined by the present application, a neoplastic cell is a cell whose normal growth control mechanism is disrupted thereby providing the potential for uncontrolled proliferation (see specification, page 13, lines 4-6). As such, tumor cells resistant to MTX or other antifolate drugs would be encompassed within the scope of neoplastic cells of the instant invention. Furthermore, by reversing the resistance to MTX and other antifolate drugs in the tumor cells, the cytotoxic sensitivity of the tumor cells to an antifolate drug is in effects enhanced.

One of ordinary skilled in the art would have been motivated to carry out the above modification because Moscow et al., Roy et al. and Kim et al. recognize that decreased folylpolyglutamate synthetase is a factor contributing to the resistance of tumor cells to methotrexate or other antifolate drug treatment, and by increasing the exogenous expression of FPGS in MTX or other antifolate resistant tumor cells, the sensitivity to antifolate drugs of the treated tumor cells would be enhanced and thereby enhancing the efficacy of traditional antifolate chemotherapy. One of an ordinary skilled artisan would have a reasonable expectation of success because Kim et al. clearly teach that lowered FPGS activity and decreased polyglutamylation of antifolates are thought to be general mechanisms by which cancer cells become resistant to a wide

range of antifolates, and that FPGS-deficient mutant Chinese hamster ovary (CHO AUXB1) cells expressing high levels of human folylpolyglutamate synthetase (FPGS) are more sensitive to the cytotoxicity of MTX compared to cells expressing lower levels of human FPGS (see Table III, page 21682). Furthermore, Roy et al. clearly show that L1210 tumor cells resistant to methotrexate or edatrexate have lowered FPGS activity.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments presented in the Amendment filed on 4/4/03 in Paper No. 15 (pages 29-34) have been fully considered.

Applicants argue basically that the Moscow patent is concerned with: (1) the RFC gene and not with the FPGS gene, (2) the restoration of MTX sensitivity to MTX resistant, transport deficient cancer cells, and not the enhancement of cytotoxicity when FPGS is expressed in neoplastic cells at a level higher than the endogenous FPGS level of said neoplastic cells. Kim shows that vector-mediated transfection of FPGS cDNA can restore FPGS activity and reintroduce cytotoxic sensitivity into variant CHO cells that express no endogenous FPGS activity, whereas the claimed invention recites that the FPGS is transferred to neoplastic cells which have some endogenous FPGS activity. Applicants further argue that examiner has not provided a sufficient explanation as to why a skilled artisan would have been motivated to modify the teachings of Kim or Garrow such that the cloned FPGS gene is delivered, not to a mutant Chinese hamster

ovary cell, but to a neoplastic cell. Applicants further noted that the claims are not dependent on any particular mechanism of action, nor do they necessarily require that the neoplastic cells be MTX resistant. Applicants' arguments are respectively found to be unpersuasive for the following reasons.

Firstly, it should be noted that this is a 103 rejection, therefore each cited reference does not have to teach every element of the claims. Examiner would like to recite a paragraph from *in re Oetiker,* 977, F.2d 1443, 1448 (Fed. Cir. 1992).

> "[T]here must be some teaching, reason, suggestion, or motivation found "in the prior art" or "in the prior art references" to make a combination to render an invention obvious within the meaning of 35 U.S.C. 103 (1998). Similar language appear in a number of opinions and if taken literally would mean that an invention cannot be held to have been obvious unless something specific in a prior art reference would lead an inventor to combine the teachings therein with another piece of prior art. This restrictive understanding of the concept of obviousness is clearly wrong.... While there must be some teaching, reason, suggestion, or motivation to combine existing elements to produce the claimed device, it is not necessary that the cited references or prior art specifically suggest making the combination.... In sum, it is off the mark for litigants to argue, as many do, that an invention cannot be held to have been obvious unless a suggestion to combine the prior art teachings is found in a specific reference."

Secondly, it should be noted that the neoplastic cells in the claims of the present invention encompass tumor cells that are MTX resistant, and that by restoring MTX sensitivity to MTX resistant neoplastic cells through the delivery and expression of an exogenous FPGS gene the cytotoxic sensitivity of MTX resistant neoplastic cells is in effect enhanced.

Thirdly, the Moscow patent teaches specifically that a short-coming of MTX (a folate antagonist) drug therapy is that previously responsive tumors (e.g. non-Hodgkin's lymphoma, child-hood acute lymphoblasti leukemia, osteosarcoma and breast cancer) can become refractory to MTX after continued exposure, and the resistance to MTX in

in vitro models can result from over-expression of the target enzyme dihydrofolate reductase, alteration of dihydrofolate reductase affinity for MTX, **decreased folylpolyglutamate synthase (FPGS)**, and decreased thymidylate synthase levels, as well as decreased MTX uptake in MTX-resistant cell lines such as murine L1210 leukemia cell lines, human leukemia cell lines, CHO cells and human ZR-75-1 breast cancer cells (col. 1, lines 10-23; lines 47-56). Furthermore, Roy et al. already teach that *in vitro* L1210 tumor cells resistant to methotrexate have a decrease in the rate of FPGS mRNA transcript formation, resulting in lower FPGS activity (page 6907, col. 2, first full paragraph), and that L1210 tumor cells resistant to edatrexate have constitutively down-regulated steady state levels of FPGS or FPGS activity compared with parental L1210 tumor cells and that FPGS mRNA from the variant cells was significantly less effective in mediating formation of the FPGS peptide product in a manner correlating with the FPGS activity or protein (see abstract). Additionally, apart from the disclosure that FPGS-deficient mutant Chinese hamster ovary (CHO AUXB1) cells expressing human folylpolyglutamate synthetase (FPGS) metabolize methotrexate (MTX) to polyglutamates characteristics of human cells (see Table I, page 21681), and that upon a short term exposure to MTX (4 h or 72 h), cells expressing higher levels of human FPGS are more sensitive to the cytotoxicity of MTX compared to cells expressing lower levels of human FPGS (see Table III, page 21682), Kim et al. teach that lowered FPGS activity may be a general mechanism by which human leukemia cells can become resistant to a wide range of antifolates (page 21684, col. 1, top 5 lines) and that decreased polyglutamylation as a mechanism for inherent MTX resistance for a number

of sarcoma and squamous carcinoma cell lines even though FPGS levels appear normal (page 21684, col. 1, bottom of the second paragraph). Therefore, it would have been obvious for an ordinary skilled artisan in the art to modify the method of Moscow as described above because Moscow et al., Roy et al. and Kim et al. recognize that decreased folylpolyglutamate synthetase is a factor contributing to the resistance of tumor cells to methotrexate or other antifolate drug treatment, and by increasing the exogenous expression of FPGS in MTX or other antifolate resistant tumor cells, the sensitivity to antifolate drugs of the treated tumor cells would be enhanced and thereby enhancing the efficacy of traditional antifolate chemotherapy.

Accordingly, claims 14-27 and 30-35 remain rejected under 35 U.S.C. 103(a) for the reasons already set forth above.

Claims 14 and 28-29 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Moscow et al. (U.S. Patent 5,763,216) in view of Roy et al. (J. Biol. Chem. 272:6903-6908, 1997; IDS); Kim et al. (J. Biol. Chem. 268:21680-21685, 1993; PTO-1449, AS) and Garrow et al. (Proc. Natl. Acad. Sci. 89:9151-9155, 1992; PTO-1449, AR) as applied to claims 14-19, 22, 25-28, 31 and 32 above, and further in view of Pawelek et al. (Cancer Res. 57:4537-4544, 1997) for the same reasons already set forth in the previous Office Action in No. 13 (pages 25-26).

The combined teachings of Moscow et al., Roy et al., Kim et al., and Garrow et al. have been discussed above. However, none of the references specifically teaches

the use of an attenuated live bacterial vector containing a nucleotide molecule encoding FPGS for enhancing the cytotoxic sensitivity of neoplatic cells to an antifolate drug.

However, at the effective filing date of the present application Pawelek et al. teach the use of an attenuated Salmonella as an anticancer vector for gene delivering into tumor cells (see abstract).

Accordingly, it would have been obvious and within the scope of skill for an ordinary skilled artisan to modify the combined teachings of Moscow et al., Roy et al., Kim et al., and Garrow et al. for delivering a DNA sequence encoding human FPGS into neoplastic or tumor cells resistant to methotrexate and other folate analogues by using an attenuated Salmonella as an anticancer gene delivery vehicle or vector as taught by Pawelek.

One of ordinary skilled artisan would have been motivated to carry out this modification because an attenuated Salmonella has been demonstrated to be an effective anticancer gene delivery vector by Pawelek et al., and that the attenuated Salmonella can proliferate and invade mammalian cells under both aerobic and anaerobic conditions such as found in solid tumors (page 4543, col. 2 bottom of the second paragraph).

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 4/4/03 in Paper No. 15 (page 35) have been fully considered.

Applicants argue basically that Pawelek does not remedy any of the fundamental defects of the rejection on claims 14-27 and 30-35. Applicants' argument is respectfully found to be unpersuasive for the reasons already set forth in the Response to Applicants' arguments on the rejection of claims 14-27 and 30-35 above.

Conclusions

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (703) 308-1906, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER